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Original Article

Overviews of reviews on patient compliance with medication protocols used in highly active antiretroviral therapy

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ABSTRACT

Purpose: To provide evidence support for the development of clinical practice guidelines regarding patient adherence to medication protocols used in highly active antiretroviral therapy (HAART) in China.

Methods: We analyzed information contained in recent systematic reviews and meta-analyses regarding patient compliance with medication protocols used in HAART.

Results: Nine systematic reviews and one meta-analysis were included in our study which involved three different aspects of patient compliance: influencing factors, assessment methods, and interventions.

Conclusions: The high quality data obtained from our study was suitable for use in developing clinically useful guidelines for patent compliance with HAART medication protocols.

1. Introduction

Acquired immunodeficiency syndrome (AIDS) is a serious infectious disease caused by the human immunodeficiency virus (HIV) [1,2]. Highly active antiretroviral therapy (HAART) is the most effective means of treating AIDS, and a patient's adherence to a HAART medication protocol is a key factor determining the success of HAART [3]. While there are numerous meta-analyses and reports concerning adherence to HAART protocols by patients in Western countries, no similar reports have been published regarding AIDS patients in China [4]. Meanwhile, people living with HIV/AIDS (PLHIV) in China have become more reliant on HAART [5]. Therefore, it is necessary to summarize the existing systematic reviews and meta-analyses related to patient compliance with HAART protocols and provide evidence needed to support the development of clinically useful guidelines for patient compliance in China. An overview of reviews is a methodology used for systematically collecting literature reviews which focus on

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the treatment, etiology, diagnosis, and prognosis of a particular disease, and then conducting a comprehensive study of the data [6,7]. Our current study summarized the existing systematic reviews and meta-analyses related patient compliance with HAART medication protocols.

2. Design and methods

2.1. Criteria for considering studies for this review

2.1.1. Types of studies

Systematic reviews and meta-analyses were included in this study. Systematic reviews of treatment protocols and traditional reviews were excluded.

2.1.2. Types of participants

HIV/AIDS positive adults, diagnosed according to Guidelines for the diagnosis and treatment of HIV-infected adults in China [8].

2.1.3. Themes

Themes related to HAART medication adherence; including influencing factors, measurement methods, and interventions.

2.2. Searching strategies

The following electronic databases were searched for relevant information starting from the date of database establishment and ending June 30, 2014: The Cochrane Library (Issue 6, 2014); The Joanna Briggs Institute Library; MEDLINE; EMbase; ProQuest; PsycARTICLES; CBM; CNKI. The main search terms were as follows: "acquired immunodeficiency syndrome/HIV/highly active antiretroviral therapy"; "adherence/persistence/compliance/dropout"; "review/meta-analysis."

We searched the reference lists of studies included in all relevant systematic reviews and meta-analyses.

2.3. Data collection and analysis

Studies were selected based on criteria separately developed by two authors of this paper (Liang Fu, Yan Hu). The third author (Hong-zhou Lu) resolved any disagreements. The full text of each article was obtained, and the data were extracted and managed using Windows Excel. The extracted information included the article title, year of publication, author, author's country/region, the number of included studies, and theme.

2.4. Critical appraisal for quality of included systematic reviews

The quality of each analyzed study was independently assessed by two authors of this manuscript (Liang Fu, Yan Hu) using the Oxman-Guyatt Overview Quality Assessment Questionnaire (OQAQ) [9,10]. The third author (Hong-zhou Lu) resolved any disagreements. Oxman et al. developed the OQAQ in 1988 for use in assessing the scientific quality of research overviews. Later, the OQAQ was adapted to include 10 items in the following 9 different areas related to study searches: search methods; comprehensive search; inclusion criteria; selection bias; validity criteria; validity assessment; methods used to combine studies; conclusion; overall scientific quality. These 9 items were either designated as appropriate or omitted based on the specific conditions used for a including a systematic review or meta-analysis. The last item (overall scientific quality) was rated on a scale of 1–7, with the score being based on the previous nine items. A higher score suggested the review or meta-analysis was of higher quality.

3. Results

3.1. Results of searching

Among 2630 studies identified in the original search; 2623 studies were written in English and 7 studies were in Chinese. Ninety-three studies were removed using Noteexpress 2.2 via duplicate checking. Additionally, 2494 studies were excluded after the title and abstract were judged to be incongruent with the study type, design, participants or theme. Another seven studies were excluded for similar reasons after reading the full text. Finally, a total of 10 studies [11–20] were included in our final analysis. A flowchart depicting our screening process is shown in Fig. 1.

3.2. Included studies

The 10 included studies involved a total of 295 subjects, and were conducted in the USA, Britain, France, Canada, and South Africa. Each study described the characteristics of the

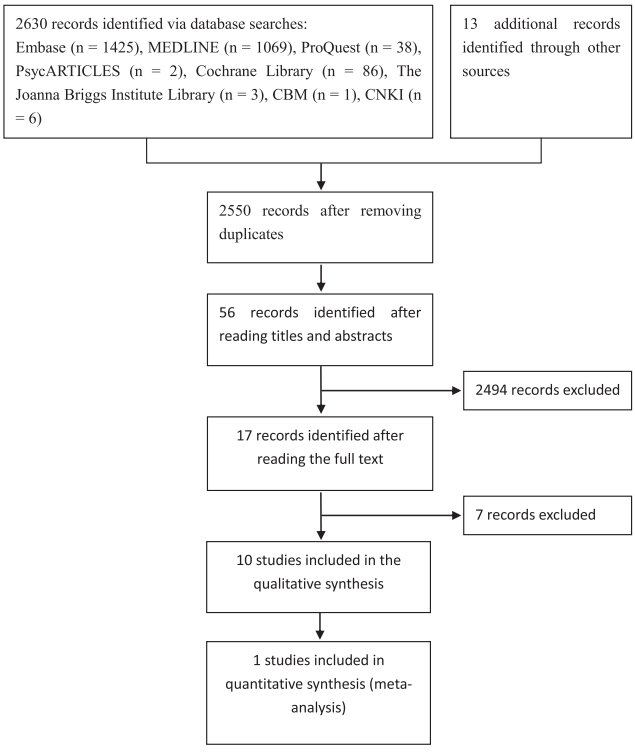

Fig. 1 – Study flow diagram.

subjects, influencing factors, assessment methods, and interventions used to maintain compliance with a medication protocol (Table 1).

3.3. Methodological quality assessment

The studies included in our analysis were assessed according to the OQAQ [9,10]. Each systematic review/meta-analysis included in our study received an overall scientific quality score between 5 and 7, suggesting a higher level of quality. Ten studies [11–20] reported search methods (I1), eight studies [11,12,14–19] conducted comprehensive searches (I2), ten studies [11–20] reported inclusion criteria (I3), six studies [11,12,15–17,19] avoided selection bias (I4), six studies [11,12,15–17,19] reported validity criteria (I5), four studies had appropriately assessed the validity of their findings (I6) [15–17,19], eight studies [11,12,14,15,17–20] reported the methods used to combine studies (I7), eight studies [11,12,14,15,17–20] used appropriate methods to combine their findings (I8), and ten studies [11–20] described conclusions supported by the reported data (I9), (Table 2).

Table 2 – Methodological quality assessment of included studies.

Studies	Items									
	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10 (Scores)
S1[11]	√	√	√	√	√	×	√	√	√	7
S2[12]	√	√	√	√	√	×	√	√	√	6
S3[13]	√	×	√	×	×	×	×	×	√	5
S4[14]	√	√	√	×	×	×	√	√	√	6
S5[15]	√	√	√	√	√	√	√	√	√	7
S6[16]	√	√	√	√	√	√	×	×	√	6
S7[17]	√	√	√	√	√	√	√	√	√	7
S8[18]	√	√	√	×	×	×	√	√	√	6
S9[19]	√	√	√	√	√	√	√	√	√	7
M1[20]	√	×	√	×	×	×	√	√	√	5

Note: S = Systematic Review; M = Meta-analysis; I = Items; √ = Sufficient; × = Omitted.

3.4. Findings

3.4.1. Factors influencing HAART medication compliance

Two systematic reviews [11,12] summarized factors (i.e., barriers and facilitators) which affected compliance with HAART medication protocols. A systematic review conducted by Mills [11] comprised 84 original studies which included 47 quantitative studies and 37 qualitative studies. The combined studies had 13,317 participants who were mainly from the USA, Brazil, Canada, Britain, and the Netherlands. The barriers to compliance reported in these studies included concerns with drug side effects (62 studies), a fear of disclosure (44 studies), forgetting to take medication(s) (38 studies), disruptions to a daily routine or a chaotic life (38 studies), and feeling low/depressed/hopeless/angry/stressed (37 studies). The facilitating factors included having a good relationship with a healthcare provider (23 studies), having social support and being comfortable with open disclosure (21 studies), a feeling of self efficacy/self meaning (20 studies), a belief in the efficacy of drugs or having faith in medical treatments (20 studies), and reminders from family/friends (19 studies). Wasti's systematic review [12] comprised 18 original which included 12 quantitative studies, 4 qualitative studies, and 2 mixed-method studies. The combined studies included 4782 participants who were mainly from India, China, and Thailand. The compliance barriers reported in those studies were financial difficulties (13 studies), concerns with drug side effects (62 studies), forgetting to take medication(s) (8 studies), being a long distance from a healthcare facility (8 studies), being too busy with other things (7 studies), and fears of stigma & discrimination (7 studies). The compliance facilitators in those studies included social support (4 studies), a feeling of self-efficacy (3 studies), and a willingness to live longer (3 studies).

3.4.2. Methods for assessing compliance with HAART medication protocols

Two systematic reviews [13,14] summarized the methods (both direct and indirect methods) used to assess patient compliance with HAART medication protocols. Marcellin's systematic review [13] comprised the results of studies with a total of 44,952 participants. Among the studies reviewed, self-reporting measures were the most commonly used methods (43 studies), followed by electronic monitoring (17 studies), and pill counts (12 studies). Some studies used additional supplementary methods including a visual analog scale (3 studies), drug plasma levels (2 studies), a pill identification test (1 study), pharmacy refill data (1 study), and unstructured patient interviews (1 study). Simoni [14] conducted a

Table 1 – Characteristics of included studies.

NO.	Included studies	Country/Region	Number of included studies	Theme
S1	Mills (2006) [11]	Canada	84	influence
S2	Wasti (2012) [12]	Britain	18	influence
S3	Marcellin (2013) [13]	France	50	assessment
S4	Simoni (2006) [14]	USA	77	assessment
S5	Young (2010) [15]	South Africa	13	interventions
S6	Hill (2012) [16]	USA	5	interventions
S7	Gentry (2013) [17]	Britain	11	interventions
S8	Amico (2006) [18]	USA	24	interventions
S9	Horvath (2012) [19]	USA	2	interventions
M1	Parienti (2009) [20]	France	11	interventions

Note: S = Systematic Review; M = Meta-analysis.

systematic review of 77 original studies which included 24,394 participants [14], and focused on the methods most often used for gathering information – self-reporting measures. The most commonly used self-reporting measure was a single item querying the number of prescribed doses the study participant had missed during a specified time period (22 studies), followed by the use of Adult AIDS Clinical Trials Group (AACTG) adherence instruments and their modified variations (15 studies), a visual analogue scale (6 studies), and the Simplified Medication Adherence Questionnaire (SMAQ; 2 studies).

3.4.3. *Interventions for improving patient compliance with HAART medication protocols*

Six systematic reviews [15–20] summarized various interventions that were used to improve patient compliance with HAART medication protocols. These included interventions performed by telephone, mobile phone text messaging, motivational interviewing, and home-based care givers. A systematic review by Horvath [19] included 2 clinical trials involving 966 PLHIV in Kenya. The results showed that any amount of mobile phone text-messaging (whether daily or weekly) was associated with greater patient compliance with HAART medication protocols when determinations were made at 48–52 weeks (RR 0.82; 95%CI: 0.72–0.94). Furthermore, text messages sent on a weekly basis (whether short or long) were also found to be effective (RR 0.78; 95%CI: 0.68–0.89). Amico's systematic review [18] comprised 24 studies involving 1999 PLHIV. The results suggested that interventions provided specifically to patients with known or anticipated problems with adhering to HAART medication protocols had only medium effects for increasing compliance ($d = 0.62$; $OR = 3.07$). Parienti's systematic review [20] of 11 clinical trials involving 3029 PLHIV revealed better patient compliance with once-daily medication regimens compared with twice-daily regimens (MD 2.9%; 95%CI: 1.0%–4.8%, $P < 0.003$). Gentry's systematic review [17] comprised 11 clinical trials involving 1381 PLHIV patients. While two of the studies indicated that telephone interventions can improve patient compliance, a meta-analysis of three other studies with sufficient data showed no significant benefit from telephone interventions (SMD 0.49; 95%CI: 1.12–2.11). Hill's systematic review [16] included 5 clinical studies with a total of 963 PLHIV. While three of the studies indicated that motivational interviewing significantly improved medication compliance, there was no meta-analysis. Young's systematic review [15] included 11 clinical studies, each involving 31 to 549 PLHIV. Two of the studies provided evidence suggesting that home-based care improved compliance with medication protocols.

4. Discussion

4.1. *There are numerous high quality systematic reviews and meta-analyses related to HAART medication adherence*

Two systematic reviews [11,12] provided high quality data suggesting that five factors predominately influenced patient compliance with HAART medication protocols. These factors were patient variables (e.g., simply forgot), beliefs about medication (e.g., side effects), daily schedules (e.g., disruptions in a daily routine/chaotic life), interpersonal relationships (e.g., negative views or lack of trust in a healthcare provider), and location of the healthcare provider (e.g., a long distance from home to the health facility). The influencing factors reported by Wang et al. [21] included the medications, patient, and societal aspects. The influencing factors reported by Luo et al. [22] included the patient, the quality of medical services, medications, and societal aspects. Our findings were similar to those reported in the above studies.

Two systematic reviews [13,14] provided high quality data indicating both that direct and indirect methods can be used to accurately assess patient compliance with HAART medication protocols. The direct methods included biological assays of the active drug(s), drug metabolites or other markers in the patient's blood, urine or other bodily fluids, while indirect methods included self-reporting measures, electronic monitoring, pill counts, and pharmacy refill data. Fu et al. [23], also summarized various methods used for assessing HAART medication compliance, including currently used direct and indirect methods, such as Adult AIDS Clinical Trails Group Adherence Instruments, Community Programs for Clinical Research on AIDS et al. Wang et al. [21], reported assessment methods which included asking the patient, various measurement techniques, and the monitoring of drug treatment effects. The results of our study agreed with those in these previous studies. High quality evidence from 6 systematic reviews [15–20] indicated that mobile phone text messaging, use of once-daily antiretroviral regimes, and identifying problems that might affect adherence with HAART medication protocols can improve patient compliance. However, there was no good evidence supporting the benefits of telephone interventions, motivational interviewing or home-based care. Effective interventions reported by Chen et al. [24], included motivational interviewing, behavioral intervention strategies (e.g., a medication reminder system), and health education, while effective interventions reported by Wang et al., included individual counseling (telephone counseling) and regular follow-ups [21]. The results in our study were similar to those in the above cited studies.

4.2. *Overviews of reviews can be a reliable means of developing guidelines for use in clinical practice*

With the development of evidence-based nursing practices in China, the number of guidelines created for use in clinical practice has significantly increased. However, most guidelines are developed without using a mature and appropriate methodology. Currently, there is a consensus that clinical practice guidelines should be developed using an evidence-based methodology. Overviews of reviews are created based on methods described in the Cochrane Handbook for Systematic Reviews of Interventions [7]. Yang et al. [25], proposed using a process which included the following eight steps: identify a problem; development of inclusion and exclusion criteria; searching studies, selecting studies; data extraction; quality assessment; data analysis; results. Our current overview of reviews was produced in strict accordance with the above requirements, and provided abundant high quality

evidence applicable for developing patient compliance guidelines for use in clinical practice. Therefore, when numerous systematic reviews and meta-analyses are available on a particular topic, we recommend using summarized evidence derived from overviews of reviews for improving the scientific quality and validity of newly developed clinical guidelines.

5. Summary

This overview of reviews included nine systematic reviews and one meta-analysis [11–20] of reports on factors which influence patient compliance with HAART medication protocols, methods of assessing compliance, and various means of intervening to increase compliance. Several highly interesting systematic reviews and a meta-analysis related to HAART medication compliance were summarized, and high-quality evidence was identified that could be used in developing clinical guidelines regarding adherence to HAART protocols.

Conflicts of interest

The authors declare no conflicts of interest.

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